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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,379	03/22/2001	Mary Gerritsen	09800081-0026	3936
23552	7590	12/15/2004	EXAMINER	
MERCHANT & GOULD PC P.O. BOX 2903 MINNEAPOLIS, MN 55402-0903			YAEN, CHRISTOPHER H	
			ART UNIT	PAPER NUMBER

1642

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/815,379

Applicant(s)

GERRITSEN ET AL.

Examiner

Christopher H Yaen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 September 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4 and 42-54 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,4 and 42-54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 9202004.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

DETAILED ACTION

Re: Gerritsen M et al
Priority Date: 22 March 2000

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/20/2004 has been entered.
2. Accordingly, claims 2, and 5-41 are canceled without prejudice or disclaimer.
3. Claims 1,3-4, and 42-54 are pending and examined on the merits.
4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

5. The Information Disclosure Statement filed 9/20/2004 is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections Maintained - 35 USC § 101 and 112, 1st paragraph

6. The rejection of claims 1,3-4, and 42-54 under 35 USC § 101 as lacking a substantial and specific well established utility is maintained for the reasons of record. Applicant argues that the instant invention does in fact have a specific and substantial

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utility. More specifically, applicant argues that the examiner's assertions of showing utility beyond a reasonable doubt is not required, but rather only that the asserted utility is more likely than not to be true. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. All the previously cited references clearly establish that one of skill in the art cannot inevitably equate the production of mRNA with the production of protein. Hence, the presumption of utility is not sufficient to satisfy the utility requirement because there is a valid and scientific reason for one of skill in the art to reasonably question the objective truth of the statement of utility.

Applicant additionally argues that the instant invention is similar to that of example 10 of the Utility Guidelines (see <http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf>, pages 54-55), indicating that the instant polypeptide of SEQ ID No: 4 is a homologue of mouse BAZF, a known transcriptional repressor. Applicant then concludes that one of skill would conclude that the human form of BAZF (i.e. SEQ ID No: 4) would naturally also function as a transcriptional repressor. Applicant additionally argues that based on this information, the use of SEQ ID No: 4 as a marker for angiogenesis would be a specific and substantial utility. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. The claims of the instant invention are drawn to an isolated polypeptide comprising the sequence of SEQ ID No: 4. After further review of the homology data obtained from the prior art search, and as stated in the prior office action mailed 3/19/2004, the credibility of SEQ ID No: 4 as being a member of the BAZF is not at

issue, but rather the utility of the instant polypeptide as a diagnostic marker is being questioned. Since nucleic acids and polypeptides are independent and distinct each from the other, credibility of utility for one invention does not necessarily merit utility for another related invention. Each claimed invention must be assessed in light of the specification. In the instant case, applicant's specification teaches that the expression hBAZF (SEQ ID No: 4) in established models of angiogenesis produced an up regulation of hBAZF mRNA in endothelial cells when compared to non-angiogenic endothelial cells. Neither the specification nor the art of record sets forth a substantial, and well established utility for the claimed polypeptide because one of skill in the art must presume that the said polypeptide exists, that said polypeptide is expressed, and that said polypeptide would predictably diagnose the presence of cancer.

Applicant's then provide prior art evidence to counter the arguments presented in the prior office actions regarding the unpredictability of correlating mRNA level to protein expression levels by arguing that RNA expression levels generally correlate to its protein expression levels. More specifically, applicant's characterize Alberts as teaching that RNA transcripts generally serve as templates for protein synthesis. Applicant's also characterize Zlot *et al* as teaching that an increase of stanniocalcin 1 mRNA correlates with an increase in its protein expression. Applicant characterizes Orntoft *et al* as teaching that there is significant correlation between DNA copy, mRNA, and protein levels. Applicant additionally characterizes Horokoshi *et al* as teaching that thymidylate synthase gene expression was directly proportional to thymidylate synthase protein expression. And finally applicant characterizes Fletcher *et al* as teaching that

there is a statistical correlation between protein abundance and mRNA abundance in yeast. From this applicant concludes that one of skill would expect that an increase in hBAZF mRNA would correlate to hBAZF polypeptide expression. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. Alberts also indicates as previously argued (see action mailed 8/8/2003) that many proteins are regulated at the translational level therefore an increase in mRNA does not necessarily indicate an associated increase in protein. Although Zlot *et al* and Horikoshi *et al* do show a direct correlation between mRNA and protein expression levels, these examples differs from the instant case because actual protein expression was assessed and measured. However in the instant case, there is no indication in the specification or in the prior art that the hBAZF (i.e. SEQ ID No: 4) polypeptide is in fact up regulated concomitantly with its mRNA, or whether there is even expression of hBAZF protein. Thus, there is no indication or evidence to refute the fact that hBAZF may or may not be regulated at the translational level as indicated by Alberts. Orntoft *et al* appear to have looked at increased DNA content over large regions of chromosomes, comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft *et al* do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding expression of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft *et al* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (see page 40).

This analysis was not done for hBAZF (i.e. SEQ ID No: 4) in the instant specification. Therefore it is unclear whether hBAZF (i.e. SEQ ID No: 4) is in a gene cluster in a region of a chromosome that is highly amplified. Therefore the relevance of Orntoft *et al* is not clear. And finally, Futchner *et al* analyzes the abundance of RNA and correlates it to the abundance of protein and indicates that it conflicts with others in the field (see pages 7364-7367), indicating the relative predictability of correlating the data RNA expression with protein expression cannot be reasonably relied on. Further, Futchner *et al* analysis is only relevant to those proteins that are abundant proteins and does not account for those that are non-abundant and possibly translationally regulated (see page 7368). Thus, given the fact that the references cited to show correlation of mRNA and protein levels are not conclusive, and given the fact that the specification provides data for detecting the differential expression between angiogenic and non-angiogenic events in endothelial cells using nucleic acid, and alleged correlation between mRNA expression levels and protein expression levels is purely speculative and represents an invitation to experiment. Thus applicant's arguments have not been found persuasive and the rejection is maintained.

Claims 1,3-4, and 42-54 remain rejected under 35 USC 112, 1st paragraph for lacking a substantial and specific well established for the reasons of record.

Claim Rejections - 35 USC § 112, 1st paragraph

7. The rejection of claims 1,3-4, and 42-53 under 35 USC § 112, 1st paragraph as lacking written description is maintained for the reasons of record. Applicant argues

that the instant specification provides sufficient written description. In particular, applicant states the amendment to claim 1 to recite functional and structural characteristics of SEQ ID No: 4, which are disclosed in the specification would obviate the written description rejection. Applicant additionally points to support for the percent homology language recited in the claims. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

The claims are drawn to an isolated polypeptide comprising an amino acid sequence having at least 84% identity with SEQ ID No: 4, wherein the polypeptide comprises a BTB/POZ domain and 5 Kruppel-like zinc finger domains. Subsequent dependent claims are drawn to increasing homology to SEQ ID No: 4. These claims are a genus claims. The specification has only provided the skilled artisan with a single embodiment of the broad genus, namely SEQ ID No: 4, and does not provide any other sequence that is encompassed by the broad genus claimed. Furthermore, the amendment to recite a structural feature does not in itself provide sufficient written description because other proteins that have the recited structural features may have widely varying and divergent functional properties. For example T'Jampens *et al* (FEBS Lett. 2002 Apr 10;516(1-3):20-6) teach that BTB/POZ domains reside in many different proteins that have diverse functions. Therefore, given the lack of disclosure of representative members of broad and variant genus, the lack of functional attributes that describe the genus, one of skill in the art cannot conclude that the applicant was in possession of the claimed genus because description of one member of the genus is not representative of the variants of the genus and is insufficient to support the claim.

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Therefore, the rejection under 35 USC 112, 1st paragraph as lacking proper written description for the broadly claimed genus is maintained.

Conclusion

8. No claim is allowed.

9. This is a continuation examination of applicant's earlier Application No. 09/815,379. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

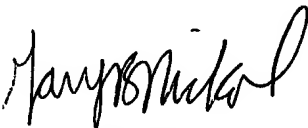
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
December 1, 2004


GARY NICKOL
PRIMARY EXAMINER